Paula Cifuentes Henderson
Patrick Dowling
Rikio Ozaki
Department of Family Medicine
University of California, Los Angeles
924 Westwood Blvd, Suite 650
Los Angeles, CA 90095-1628

Correspondence to:
Dr Henderson
paulahenderson@mednet.ucla.edu

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Should all patients with diabetes mellitus be screened for hemochromatosis?

CASE HISTORY

The patient, a 46-year-old white man, was admitted to the hospital because during the past 4 months he had progressive nausea and vomiting and a marked weight loss of 31.8 kg (70 lb). Months before admission, the patient noted increased thirst to the point that during the 3 days before admission, he was requiring ten to fifteen 64-oz bottles of a soft drink per day. On the day of admission, the patient had emesis, some epigastric discomfort, generalized weakness, malaise, and lightheadedness.

His medical history was notable for obesity and hypertension; he denied any recent use of alcohol, drugs, or any medications. He had no previous hospitalizations. He had no family history of diabetes; his father had hypertension, and a sibling probably had liver disease.

On admission, the patient's temperature was 36.6°C (97.9°F); respirations, 24 per minute; pulse rate, 120 beats per minute while lying and 148 while standing;

and blood pressure, 122/84 mm Hg. He appeared tachypneic but was alert and oriented. The findings of the rest of the general physical examination were normal. A finger-stick blood glucose test (Accucheck) gave a reading of 500 mg/dL [27.8 mmol/L]. He had a bicarbonate concentration of 10 mmol/L, an anion gap of 17, and the serum specimen revealed ketones. Arterial blood gas values with the patient breathing room air were pH of 7.07, P_{CO_2} of 14.9 mm Hg, P_{O_2} of 144 mm Hg, oxygen saturation of 98.7%, bicarbonate of 7.4 mmol/L, and a base excess of −24.

An abdominal computed tomographic scan was obtained, given the presentation of diabetic ketoacidosis and the pronounced weight loss in this previously healthy man (figure 1). The scan showed a normal pancreas and a nonspecific homogeneously and slightly increased density throughout the liver.

Further diagnostic tests and a liver biopsy were performed. The liver core biopsy specimen demonstrated hemochromatosis; iron was found within hepatocytes, with the greatest accumulation in the periportal zones. Diminished staining was evident toward central zones. A genetic test for the *HFE* gene was then performed (see below); the results confirmed the diagnosis of hemochromatosis—the patient being found homozygous for the *C282Y* mutation (cysteine-to-tyrosine substitution at nucleotide 282). Once his diagnosis was confirmed, we contacted members of his family and recommended that they have screening serum tests for phenotyping and genetic testing, looking for the *HFE* gene as well. His father was found to be homozygous for *C282Y* and had had both knees replaced due to osteoarthritis and a pacemaker fitted. His oldest brother, who had "some liver problem," was also homozygous for *C282Y*. His homozygous sister was asymptomatic, and his heterozygous brother had no phenotypic manifestations or any other symptoms related to hereditary hemochromatosis (HHC).

METHODS

For this evidence-based case review, we reviewed the literature on the natural history of hemochromatosis, its clinical presentation, data on the *HFE* gene, and implications of this gene for health policy, such as whether to offer genetic screening. We searched the literature by using the Internet to access the web sites of the National Institutes of Health, the Centers for Disease Control and Prevention (CDC), and the Cochrane Library. We included randomized controlled trials from the past 5 years and systematic reviews of case-control studies. Cross-sectional studies were included to give the prevalence of the condition. The studies identified in the search were reviewed and selected after critically appraising the abstracts using the criteria of Jadad.[1]

THE CLINICAL QUESTIONS

What is the prevalence of HHC, and what groups are at highest risk?

Hereditary hemochromatosis is the most common genetic metabolic disorder among people of northern European

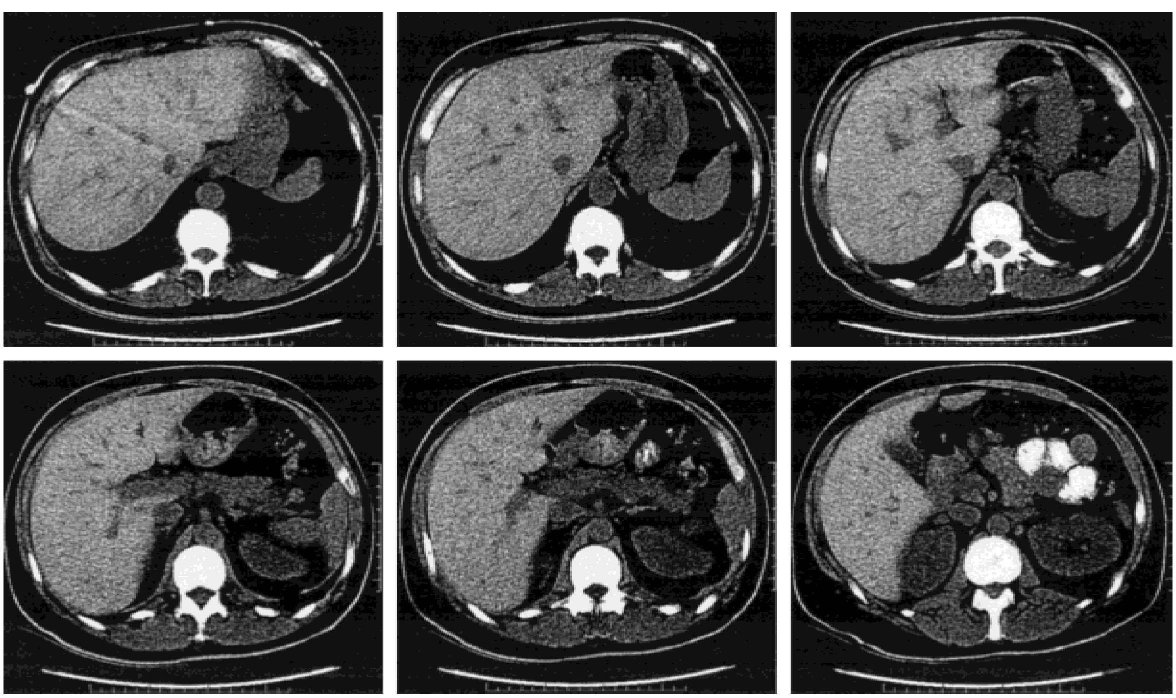

Figure 1 Abdominal computed tomographic scan showing a normal pancreas and a nonspecific, homogeneously slightly increased density found throughout the liver.

ancestry. About 1 of 250 people among the US white population are homozygous for the *C282Y* mutation, and 1 of every 10 people are carriers.[2-4]

This autosomal recessive disorder was first described by Trousseau in 1865. The disorder is associated with excessive amounts of iron that deposit in the liver, pancreas, joints, heart, and other organs. In 1977, Simon and colleagues established the genetic basis of this disease as an association between HLA and a predisposition to the disease.[5] As a result of the identification of the gene for HHC, the number of patients with no clinical manifestations in whom the disorder is being diagnosed at an early stage is significantly increasing.

What are the clinical features of HHC?

The classic presentation of HHC used to be bronze diabetes, or diabetes mellitus with hyperpigmentation of the skin and liver cirrhosis. Other clinical manifestations include fatigue, malaise, arthralgias and arthropathy, hepatomegaly with elevated aminotransferase levels, hypogonadism, impotence, hypothyroidism, and cardiomyopathy.[6] Because the presentation is often nonspecific, clinicians must maintain a high index of suspicion.

What tests should be performed to detect and to confirm the diagnosis of HHC?

The earliest phenotypic manifestation in HHC is an elevated transferrin saturation. Although this is the best initial screening test, debate exists about the appropriate cutoff for diagnosing HHC. In practice, a fasting transferrin saturation of 45% or greater identifies virtually all affected homozygous persons as well as many who are not affected.[7]

Until recently, the next diagnostic step would include a liver biopsy to further characterize patients with abnormal results of iron studies. The iron load can be quantitated subjectively with the use of a Prussian blue stain and objectively by the calculation of the hepatic iron index, which has been considered one of the most sensitive and specific tests for establishing the diagnosis of HHC.[8,9] With the discovery of the *HFE* gene, however, first reported in 1996,[10] testing for the gene may be the most appropriate initial confirmatory test in some patients. It is also an extremely useful tool for screening the relatives of an identified proband.

What is the role of genetic testing?

The *HFE* gene, located in the short arm of chromosome 6, encodes a major histocompatibility complex (MHC) class I protein. Many mutations have been identified: one results in the change of cysteine to tyrosine at position 282 (Cys282Tyr), a second results in a change in histidine at position 63 to an aspartate (His63Asp),[11] and another (*S65C*) may increase the risk of iron overload.

Many publications in the medical literature describe the *HFE* genotypes in patients with hemochromatosis, and the homozygous *C282Y* genotype seems to be associated with the greatest risk for iron overload.[3,12-14] The importance of other *HFE* mutations is controversial. The risk of developing iron overload for persons with these other *HFE* mutations is unknown. The studies that quantify this risk calculate the odds ratio for the development of iron overload for each genotype compared with the homozygous *C282Y.* These studies found that homozygosity for *C282Y* was associated with the greatest risk (odds ratio, 2,300), followed in order by compound heterozygosity (*C282Y/H63D*), *H63D* homozygosity, *C282Y* heterozygosity, and last, *H63D* heterozygosity, which was associated with the lowest risk (odds ratio, 1.6).[15]

Even though genetic testing could be implemented for population-based screening, it is still not practical (see below), nor is it cost-effective. This is because of uncertainties about prevalence and penetrance of *HFE* mutations and the optimal care of asymptomatic people carrying the mutation.[15,16] The gene test is most useful at the moment for screening family members of an identified proband. Also, in some cases *HFE* gene testing may eliminate the need for liver biopsy—that is, for patients with evidence of iron overload who are *C282Y* homozygous, a liver biopsy may be unnecessary to confirm the diagnosis of HHC.

Should patients with diabetes and the general population be screened for hemochromatosis?

Early diagnosis of hemochromatosis might be expected to reduce the burden of the disease. However, diabetes is a

Strategies to prevent iron overload disease

	Enhanced case findings	Universal screening
Advantages	• Occurs in the usual health care setting • Accessible follow-up • Lower number of persons tested • Less false-positive tests	• Detection before the onset of any symptoms • Greater impact on the reduction of the avoidable complications of HHC
Disadvantages	• Could miss patients with early symptoms • Initiation of treatment might be too late to achieve full benefits of early phlebotomy	• More false-positive results • More persons exposed to psychological, social or economic consequences • Additional resources required

common disease, and the penetrance of the *HFE* mutation and the optimal care of asymptomatic people carrying this mutation are uncertain. Screening diabetic patients for the *HFE* mutation has many implications, including the possible social, economic, and psychological effects that the diagnosis of HHC can carry. Accordingly, the current recommended approach to the prevention of iron-overload disease could be divided into 2 possible strategies[17]: enhanced case finding (this strategy justifies screening diabetic patients for iron overload) versus universal screening of all patients (not justifiable) (see box).

Enhanced case finding

Enhanced case finding becomes the first stage in a public health response when evidence has emerged for an effective early treatment of a disorder. It means the detection of HHC at the time of early symptoms, and it allows patients to benefit from early phlebotomy.

The nonspecific symptoms of HHC are relatively common among all people, and some of the morbidity in screening studies could be due to other causes. It is, therefore, possible that only a subset of persons detected in this program would develop disorders attributable to iron overload. Furthermore, because transferrin saturation screening leads to treatment, prospective follow-up in itself cannot be used to determine the proportion of persons testing positive for the disorder who would remain healthy over time if untreated.

The implementation of this approach would include adding fasting serum transferrin saturation to the usual workup of patients with newly diagnosed diabetes mellitus, arthritis, and impotence (figure 2).[16] The CDC recommends such iron-overload testing in anyone with possible symptoms of hemochromatosis, which includes patients with newly diagnosed diabetes mellitus (see below).

Universal screening

Before implementing universal screening, we would need more evidence of benefit because it involves the testing and treatment of healthy people without any medical complaints. Despite all possible benefits that this could offer, the CDC does not recommend universal screening for HHC because of many unresolved issues.[14,18]

What do the CDC guidelines say about screening for iron overload?

The guidelines state the following[18]:

> The CDC currently recommends iron overload testing for persons who have a close blood relative with hereditary hemochromatosis, because they have a substantial risk of developing clinical complications and represent an ideal group for targeted prevention efforts. In addition, persons experiencing the unexplained symptoms compatible with hemochromatosis (these symptoms include severe weakness or fatigue; unexplained joint or abdominal pain; signs of liver disease, diabetes, or heart problems; impotence; infertility; and loss of menstrual periods) should also be tested. Testing to exclude other causes of these medical problems should also be performed. Persons with elevated iron or liver function measures should be monitored by their health care provider. Strategies are needed to disseminate information to family members about their genetic risk and to aid their efforts to be tested. This challenge must be accomplished in the course of patient care. Educational efforts are needed to heighten awareness of the genetics of iron overload and prevention opportunities among family members. To this end, CDC, in collaboration with other partners, is developing a national education campaign to heighten health care providers' awareness of the need for early diagnosis and treatment of iron overload due to hereditary hemochromatosis.

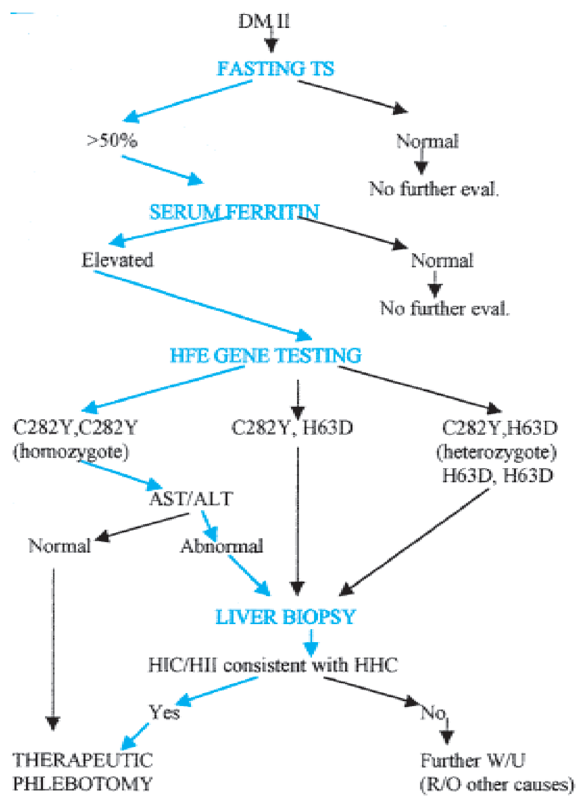

Figure 2 Screening algorithm for hereditary hemochromatosis in patients with type 2 diabetes mellitus (DM II). TS = transferrin saturation; AST/ALT = aspartate aminotransferase and/or alanine aminotransferase; HIC = hepatic iron concentration; and HII = hepatic iron index.

What is the most effective management of HHC?

Physicians' responsibility is not only to provide patients with adequate treatment but also to ensure that family screening is performed.[19] The treatment of HHC is safe, simple, inexpensive, and effective (suggested by clinical observations) in preventing the complications of iron overload.

Patients should undergo weekly phlebotomy of 500 mL of whole blood (equivalent to about 250 mg of iron). Therapeutic phlebotomy should be initiated in men with serum ferritin levels of 300 µg/L or more and in women with serum ferritin levels of 200 µg/L or more, regardless of the presence or absence of symptoms. It should be continued until patients develop iron-limited erythropoiesis—that is, when the patient's hematocrit fails to recover before the next phlebotomy, the transferrin saturation is more than 50%, and serum ferritin levels are less than 50 µg/L.[10] Once this initial therapeutic phlebotomy is completed, patients will require maintenance phlebotomy of 1 unit of blood every 2 to 3 months, although some patients do not reaccumulate iron.

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Linda E Pinsky
Department of Medicine
Division of General Internal Medicine
University of Washington Medical Center
4245 Roosevelt Way NE
Seattle, WA 98105-6920

Giuseppina Imperatore
Division of Diabetes Translation
National Center for Chronic Disease Prevention and Health Promotion
Centers for Disease Control and Prevention
Atlanta, GA

Wylie Burke
Department of Medical History and Ethics
University of Washington School of Medicine

Correspondence to:
Dr Pinsky
lpinsky@u.washington.edu

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